C. Remarks/Argument

Reconsideration of this application is respectfully requested. Claims 1-55 are pending. Claims 8, 11-14, and 16-55 are withdrawn as directed to nonelected inventions. Applicants hereby request rejoinder of these withdrawn claims, some of which have been amended to depend from a corresponding composition claim. *See* MPEP §821.04 and 37 C.F.R. § 1.104.

In the Office Action, claims 1-7 and 9-10 were rejected under 35 U.S.C. §112, first paragraph, as containing subject matter that was not described in such a way as to enable one skilled in the art to make and/use the invention. The Office Action also included an objection to claim 1 on grammatical grounds.

In response to the rejection, claim 1 is amended to recite that the peptide consists of 2 to 15 amino acid residues. Claim 1 is further amended to add the preposition "of" in response to the objection on grammatical grounds.

The Examiner stated in the Office Action: "Thus, one must begin with an infinite array of lipopeptides, then determine which of them exhibit antibacterial, antifungal or anticancer activity. For each of those that exhibit the activity, one must then remove the fatty acyl group, and measure the activity (antibacterial, antifungal or anticancer) of the deacylated peptide, and then determine which of those deacylated peptide exhibit lower activity than the corresponding acylated peptide. The assertion here is that to do all of this for an infinite number of peptides would require "undue experimentation"" (page 3 of the pending Office Action).

The present invention discloses the surprising finding that inactive or weakly active antibacterial, antifungal and/or anticancer peptides having a net positive charge that is equal or greater than +1 comprising at least two positively charged amino acid residues, exert improved or even superior antibacterial, antifungal, and/or anticancer activity after being conjugated to a fatty acid (see paragraph [0014] and [0051] of the published application). The specification explicitly discloses that "In order to improve the cytolytic activity of L-amino acid peptides or diastereomeric peptides against fungi, or to modify an inactive peptide such that it will be active against fungi and/or bacteria and/or tumor cell, fatty acids (having variable lengths) were attached to the peptides" (paragraph [0051] of the published application). Thus, according to the present invention, one begins with inactive or weakly active antimicrobial and/or anticancer

peptides (see paragraph [0018] of the published application). The Examiner is therefore erred in his assertion that "one must begin with an infinite array of lipopeptides" (page 3 of the pending Office Action; underline is added for emphasis). It should be emphasized that according to the present invention, one begins with peptides that show the following features: (i) the peptide must comprise at least two positively charged amino acid residues: (ii) the peptide must have a net positive charge that is equal or greater than +1; and (iii) the peptide must be devoid or have weak antimicrobial and/or anticancer activity (see paragraph [0015] and [0053] of the published application). According to the principles of the present invention, only peptides that fulfill these three features are then conjugated to a fatty acid so as to endow these peptides with antibacterial and/or antifungal and/or anticancer activity (see paragraph [0014] of the published application). Thus, there is a limited number of peptides which fulfill these three features. In order to further establish that the present invention discloses a limited number of peptides, claim 1 has been amended to include the recitation that the peptide consists of 2 to 15 amino acid residues, support for which can be found at paragraphs [0017] and [0019] of the published application. Thus, currently amended claim 1 is clearly directed to a limited number of peptides that fulfill the three features listed above, as well as an additional feature, i.e., the length of the peptide.

It should therefore be understood that, according to the present invention, one begins with inactive or weakly active antimicrobial and/or anticancer peptides and then conjugates a fatty acid to these peptides to obtain active lipopeptides, not vice versa, as stated by the Examiner in the pending Office Action.

The Examiner referred to Clark C. R. (J. Med. Chem. 30(7): 1214-1218, 1987) referred to hereafter as "Clark". The Examiner stated that acylation of the amino group of compound 1 eliminated anticonvulsant activity.

Clark discloses amides and amines related to 4-amino-N-(1-phenylethyl) benzamide (compound 1). These amides and amines lose most of their anticonvulsant activity after acylation and alkylation. As indicated by the Examiner, anticonvulsant activity is not the same as antimicrobial or antitumor activity. Although one cannot compare anticonvulsant activity with antimicrobial or anticancer activity, even if these activities were comparable, the amides and amines of compound 1 disclosed by Clark are active anticonvulsant compounds, while the peptides of the present invention are inactive or weakly active antimicrobial and/or anticancer

peptides. Thus, one cannot refer to Clark as implying the unpredictable effect of fatty acid conjugation to inactive or weakly active antimicrobial and/or anticancer peptides.

The Examiner referred to Creemer L. C. (J. Med. Chem. 39(25): 5021-5024, 1996) referred to hereafter as "Creemer". The Examiner stated that Creemer discloses that acetylation of compound 7 eliminated antitumor activity.

Creemer discloses C-11 esters of wortmannin. These esters showed increased cell cytotoxicity in leukemia cell line when compared to wortmannin. Thus, the C-11 esters of wortmannin are active cytotoxic compounds. In contrast, the peptides disclosed in the present invention are inactive or weakly active antimicrobial and/or anticancer peptides. Moreover, it should be indicated that wortamannin is not a peptide. Thus, one cannot refer to Creemer as implying the unpredictable effect of fatty acid conjugation to inactive or weakly active antimicrobial and/or anticancer peptides.

The Examiner refers to Uehara Y. (Journal of Antibiotics 29(9): 937-943, 1976) referred to hereafter as "Uehara". The Examiner stated that Uehara discloses that acylation of negamycin results in loss of antibacterial activity.

Uehara discloses analogs of negamycin, a well known antibiotic. In contrast, the peptides disclosed in the present application are inactive or weakly active antimicrobial and/or anticancer peptides. Moreover, negamycin is not a peptide. Thus, one cannot refer to Uehara as implying the unpredictable effect of fatty acid conjugation to inactive or weakly active antimicrobial and/or anticancer peptides.

The Examiner refers to Scott H. (Anti-Cancer Drug Design 11(6): 451-462, 1996) referred to hereafter as "Scott". The Examiner stated that Scott discloses that compound 11 was inactive in an assay of anti-tumor activity, thus providing an example where conjugation of a pharmacologically active anti-tumor agent to a lipophilic group resulted in a reduction of activity.

Scott discloses conjugates of N^4-hexadecyl-1-β-D-arabinofuranosylcytosine (hxd^4araC) to phospholipids. Scott further discloses that hxd^4araC is a cytostatic derivative of the well known 1-β-D-arabinofuranosylcytosine (araC) antileukemic drug. In contrast, the peptides disclosed in the present application are inactive or weakly active antimicrobial and/or anticancer peptides.

Moreover, hxd^{4}araC is not a peptide. Thus, one cannot refer to Scott as implying the unpredictable effect of fatty acid conjugation to inactive or weakly active antimicrobial and/or anticancer peptides.

Trani A (Il Farmaco 51(7): 503-512, 1996) referred to hereafter as "Trani". The Examiner stated that Trani discloses that acylation of purpuromycin causes a reduction in antimicrobial potency.

Trani discloses derivatives of 4-purpuromycin, which is a natural antibiotic. In contrast, the peptides disclosed in the present application are inactive or weakly active antimicrobial and/or anticancer peptides. Moreover, purpuromycin is not a peptide. Thus, one cannot refer to Trani as implying the unpredictable effect of fatty acid conjugation to inactive or weakly active antimicrobial and/or anticancer peptides.

The Examiner refers to Avrahami (Biochemistry 41: 2254-2263, 2002) referred to hereafter as "Avrahami". The Examiner stated that Avrahami discloses that N-palmitoyl magainin is no more effective than magainin itself against *C. albicans* and *A. fumigatus*.

Avrahami discloses a magainin analog that is a potent antibacterial peptide consisting of 23 amino acid residues. In contrast, the peptides disclosed in the present application are inactive or weakly active antimicrobial and/or anticancer peptides consisting of 2-15 amino acid residues. Thus, one cannot refer to Avrahami as implying the unpredictable effect of fatty acid conjugation to inactive or weakly active antimicrobial and/or anticancer peptides.

The applicants respectfully disagree with the Examiner's assertion that even if it were possible to determine, absent of undue experimentation, which lipopeptides will exhibit antibacterial, antifungal or anticancer activity, one would still be left with the fact that removal of the acyl group does not predictably result in a reduction of activity.

As discussed above and recited in currently amended claim 1, the present invention is directed to a lipophilic conjugate that comprises an inactive or weakly active antimicrobial and/or anticancer peptide coupled to a fatty acid, wherein the inactive or weakly active peptide consists of 2 to 15 amino acid residues, has a net positive charge that is equal or greater than +1, and comprises at least two positively charged amino acid residues. Conjugation with the fatty

acid endows the peptide with antibacterial and/or antifungal and/or anticancer activity (paragraphs [0014] and [0051] of the published application).

The present invention clearly discloses that conversion of these inactive or weakly active antimicrobial and/or anticancer peptides to active antimicrobial and/or anticancer peptides requires that they be conjugated to a fatty acid. One does not begin with lipopeptides that exhibit antibacterial, antifungal, or anticancer activity, and then removes an acyl group so as to obtain peptides having reduced activity.

The current amendment of claim 1 serves to address the Examiner's rejection and to more particularly point out and distinctly claim the invention. The applicants respectfully request withdrawal of the rejection under 35 U.S.C. §112 and issuance of a Notice of Allowance. Also, because Applicants have herein requested rejoinder of the withdrawn claims and have amended those claims to be dependent upon the product claims herein, a Notice of Allowance is also respectfully requested for the withdrawn claims. Should any questions or issues arise concerning the application, the Examiner is invited to contact the undersigned at the telephone number provided below.

This response is due on or before December 8, 2008. The Commissioner is hereby authorized to charge payment of any additional fees that may be required, or credit any overpayment of same, to Deposit Account No. 08-1935, Reference No. 2488.031.

Respectfully submitted,

Dated : December 8, 2008

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